Chapter 1

Introduction

General Background

Starch has played a crucial role in human daily lives since time immemorial. Primarily recognized as food, starch has then been widely used for other purposes, for example, colored and uncolored starches were used as cosmetics, uncolored starch was used principally as a hair powder, and as whitening agent in textile industry. As civilization progressed and expanded, the industrial use of starches spread and new plant sources evolved. Wheat, barley, and potato starches were commonly used in Europe and United States, while rice starch has been produced in substantial quantities in Asia. Tapioca and corn have recently become the prime sources of starch throughout the world (Whistler, 1965). In Thailand, rice starch and glutinous rice starch are major starches cultivated for consumption, while tapioca starch is produced substantially for export.

The use of starch in pharmaceutical industry as an ingredient in drug formulation has been increased. Because of its low cost and chemically inert, starch is considerably a candidate in almost every types of additive in the formulation. In Thailand, the abundance of starches has promoted the research interests in the application of starch as an ingredient in several drug dosage forms. However, these

applications have been limited as their characteristics may not be pertinent to the specific uses purposed. For example, its insufficient flowability prevents the use as directly compressible binder and its poor swelling property made it impossible to be used as a suspending agent.

The introduction of modified starches and starch derivatives has enhanced the research attempts in pharmaceutical preparation to overcome the problems that occurred from the limit uses of starch. Unlike the native starch, modified starches and starch derivatives possess several characteristics that allow them to be employed more extensively as ingredients in drug formulation than native starch. Particularly in solid dosage form, starch was modified by chemical, physical, or physico-chemical treatments to obtain a superdisintegrant (Thavisak Teruya, 1995), directly compressible vehicle (Siriyos Tamaroon and Poj Kulvanich, 1992; Wallop Weecharangsan, 1995), binder in tablet formulation in form of cold water swellable paste (Tasana Pitaksuteepong, 1995). Starch derivatives were used as crosslinking agents in preparations of microcapsule. These characteristics, including the improvement in flowing, compressing, and disintegrating properties, have been investigated to evaluate modified starches and starch derivatives as binder and disintegrant (Visavarungroj, Herman, and Remon, 1990a; Visavarungroj and Remon, 1990b, 1991).

The properties of chemically modified starches or physically modified starches are varied depend on the modification methods and the control of condition while the

modification takes place. The properties of starch are also depended on the ratio of amylose/amylopectin which varies among different plant species and sources. This leads to the attempts of modifying various natural starches in order to obtain compounds that possess appropriate properties as suspending agent.

Several studies have been engaged toward this direction. The sodium salts of O-carboxymethyl derivatives of potato starch with degree of substitution below 0.5 were prepared and evaluated for viscosity, suspending and emulsifying properties by Mishra, Jain, and Agrawal (1990). While the emulsifying properties could not be observed in this study, the suspending properties of these modified starches have been characterized. It was showed that the suspending nature of modified starch reduced evidently with increasing in degree of substitution due to increase in solubilization of the derivative. The result from this study suggested that modified starches could be developed as commercial suspending agent.

In the most recent work, Tasana Pitaksuteepong (1995) studied the properties of five modified starches including rice starch, glutinous rice starch, tapioca starch, corn starch, and potato starch as tablet binder. The result of the study revealed that glutinous rice starch possessed the best binding property among all 5 modified starches being investigated.

This study is a consequent research of the works mentioned above. The purpose of the study is focused on the evaluation of modified starches as suspending

agent. Four domestically available starches, including tapioca starch, rice starch, glutinous rice starch, and corn starch, were chemically modified by the substitution reaction with carboxymethyl group to yield modified starches with 3 different degrees of substitution. These modified starches were examined and evaluated for their suspending properties. Selected modified starches were employed as suspending agent in a development of suspension formulation using ibuprofen as a model drug.

<u>Objectives of this study</u>

1. to modify a number of domestically available natural starches by the substitution reaction with carboxymethyl group in order to obtain an appropriate sodium carboxymethylstarch with suspending properties

2. to compare some characteristics of modified starches obtained from several types of starches as well as to determine an optimum degree of substitution that will be used as a suspending agent for each type of starch

3. to compare the suspending properties of the prepared modified starches with other commercially available suspending agents

4. to employ the most appropriate modified starch in this study as a suspending agent in a development of suspension formulation using ibuprofen as a model drug

Literature Review

Starch is a homopolymer of D-glucose in which 96% or more of the D-glucose units are linked α-D-(1-->4) and 4% or less are linked α-D-(1-->6). Furthermore, all D-glucose units which are linked α-D-(1-->6) are also linked α-D-(1-->4). This evidence is interpreted to mean that starch is primarily a branches polymer consisting of D-glucose units linked α-D-(1-->4) with branches at the C-6 position on an average of once every 26 or more D-glucose units. This evidence further supports the concept that starch may be either a homologous branched polymer or a heterogeneous mixture of branched and linear polymers. The unbranched component of starch is called amylose and the branched component is called amylopectin.

Amylose

Amylose is mainly a linear polymer of α-D-glucopyranosyl units linked (1-->4) as shown in Figure 1. This polymer may be separated from the starch by complete gelatinization and vigorous dispersion of the hot starch solution with a complexing agent. The glucose unit contains one primary, two secondary hydroxyl groups, and an aldehydic group in the form of an inner hemiacetal, which is the reducing end of the molecule. The opposite end, or nonreducing end, contains an anhydroglucose unit containing one primary hydroxyl group and three secondary hydroxyl groups. The other anhydroglucose units contain one primary and two secondary hydroxyl groups.

The abundance of hydroxyl group imparts hydrophilic properties to the polymer, giving it an affinity for moisture and dispersibility in water. However, because
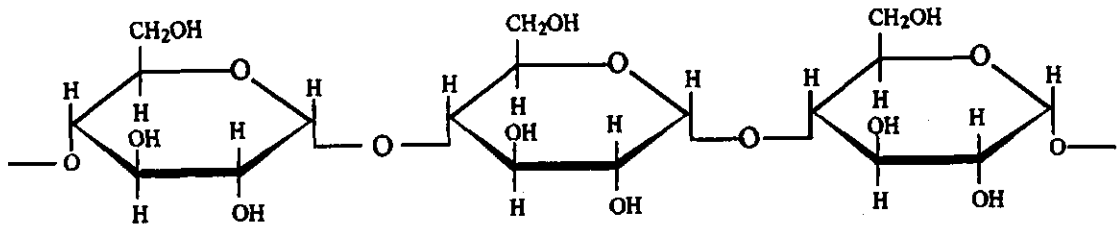
CH₂OH ... structure labels

Figure 1   Structure of Amylose Molecule

of their linearity, mobility, and hydroxyl groups, amylose polymers have a tendency to orient themselves in a parallel fashion and approach each other closely enough to permit hydrogen bonding between hydroxyl groups on adjacent polymers. As a result, the affinity of the polymer for water is reduced and the sol becomes opaque.

Amylopectin

Amylopectin is a highly branched polymer containing, in addition to anhydroglocose units linked together as in amylose through α-D-(1-->4) glucosidic bonds, periodic branches at the C-6 position. These branches are linked to the C-6 by α-D-(1-->6) glucosidic bonds. Each branch contains about 20 to 30 anhydroglucose units. The structure of amylopectin molecule is illustrated in Figure 2.

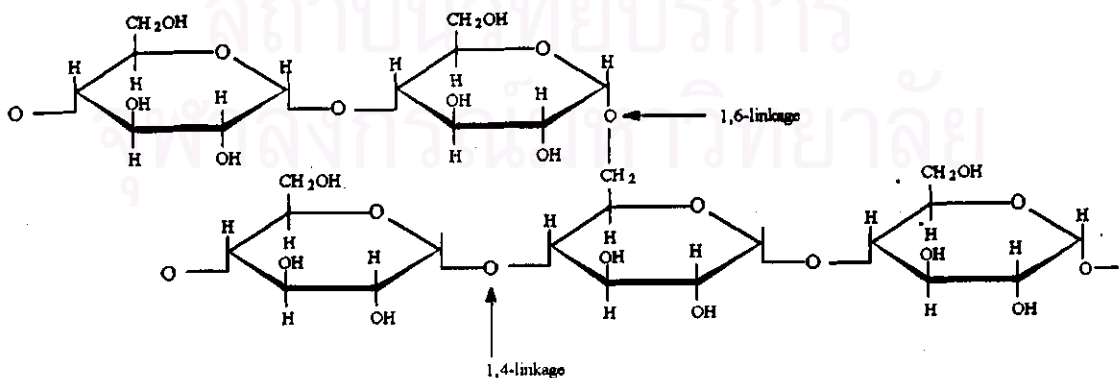1,6-linkage

1,4-linkage

Figure 2   Structure of Amylopectin Molecule

The large size and branched nature of amylopectin reduce the mobility of the polymers and interfere with any tendency for them to become oriented closely enough to permit significant levels of hydrogen binding. As a result, aqueous sols of amylopectin are characterized by clarity and stability as measured by resistance to gelling on aging.

Variation of Amylose Content in Starches from Different Plant Species

Starch could be obtained from different plant sources. The range of amylose content in different plant species was varied. This variation contributes to the different in properties with respect to the uses as additives in dosage forms. Table 1 is a partial list of starches, their plant sources, and their amylose contents.

Table 1   Types of Starches and Their Sources and Amylose Contents (Hullinger, 1960; อรรควุฒิ ทัศน์สองชั้น, 2529)

Type of Starch	Source	Amylose (%)
Corn or Maize	mature grain of Zea mays	22-28
Wheat	mature grain of Triticum aestivum	17-27
Barley	mature grain of Hordeum vulgare	24-27
Potato	tuber of Solanum tuberosum	23
Oat	mature grain of Avena sativa	23-24
Rice	mature grain of Oryza sativa	16-17
Glutinous Rice	mature grain of Oryza sativa (var.glutinous)	0-5
Tapioca or Cassava	tuber of Manihot esculenta	17-22

Schwartz and Zelinskie (1978) studied the binding properties of the corn starch fractions amylose and amylopectin and concluded that the binding properties of starches were due to amylopectin fraction while the amylose fraction was responsible for the disintegrant properties. With the exception of the waxy starches that consist only of amylopectin, it has been found that nearly all starches contain 20-30% of the linear component, amylose.

Modified Starches and Starch Derivatives

Modifications of native starches are carried out to provide products with the properties required for particular uses. These modifications can be achieved by either chemical, physical, or physico-chemical procedures. Starch derivative is a chemically modified starch in which the chemical structure of some of the glucose units has been altered. This definition excludes acid-modified starches but includes all oxidized starches. Starch derivatives are characterized by the nature of their chemical modification, degree of modification, degree of polymerization and physical form. Starches, as polyhydroxy compounds, undergo many reactions characteristic of alcohols, including esterification and etherification. Substitution of the hydrogen atoms of starch hydroxyl groups yields starch esters, both organic and inorganic, and starch ethers; oxidation at C-2, C-3 or C-6 produces oxidized starches; attachment of polymeric chains to the starch molecule leads to graft copolymers; and treatment of starch with molecules having more than one reacting group usually results in intermolecular derivatives known as cross-linked or cross-bonded starches.

The degree of chemical modification may be expressed in several ways. If the modification involves substitution at the hydroxyl groups, the average number of substituents per anhydroglucose unit is the degree of substitution (DS). A DS of 1.0 indicates an average of one substituent for each anhydroglucose unit; since the D-glucopyranosyl monomers contain, on average, three free hydroxyl groups, the maximum possible DS is 3.0 (Shah et al, 1981).

Sodium O-Carboxymethyl Starch Ether

Highly water-soluble carboxymethyl starch ether, usually obtained as the sodium salt, is manufactured by the reaction of starch with etherifying agent, chloroacetic acid or sodium chloroacetate, in the presence of aqueous sodium hydroxide. Several procedures employing these alkylating agents have been reported (Wu, Gan, and Chen, 1993; Zhang et al, 1993) and patented (Filbert, 1952). The reaction is believed to occur in the manner shown in Figure 3. Although the product is referred to as a sodium salt of carboxymethylstarch ether, a small amount of acid carboxymethylstarch ether is also presented.
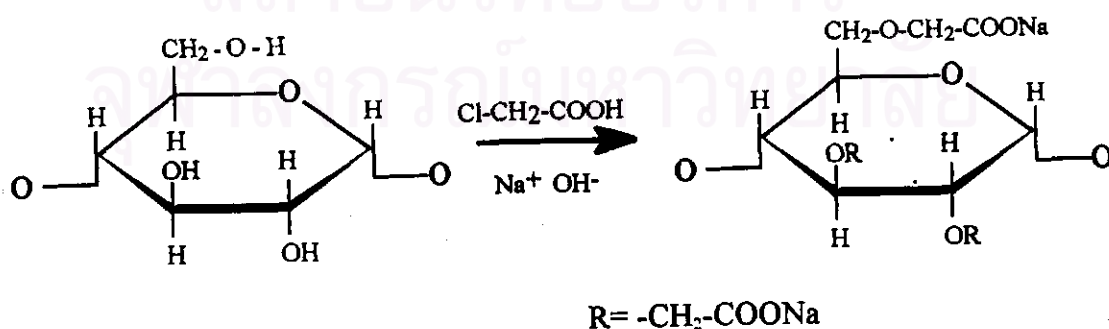
Figure 3   Sodium O-Carboxymethylation Reaction of Starch

A major improvement in carboxymethylation technique involves conducting the reaction in a water-miscible solvent containing minor amount of water. Both methanol and ethanol have been widely used as solvent. The viscosity of carboxymethylstarches may be increased by the incorporation of various cross-linking agents in the reaction mixture.

Commercial utility of carboxymethylstarch, if economically produced, is the textile and paper manufacturing industry. Its use in textile finishing and dyeing has been demonstrated; and because of its resistance to biological degradation, it has been considered as a warp size that would not contribute to the biological oxygen demand of the waste stream from a desizing operation. Other major industrial applications proposed for carboxymethylstarch are as soil suspending agents in detergents and as flocculants. One of the oldest miscellaneous uses for carboxymethylstarch is as an indicator in iodometric titrations due to its superiority over starch. Other uses include soil conditioner, component of latex-based paint and of a paint remover, binder for kaolin castings, replacement of gum arabic in lithography, component of photographic film emulsion, and additive to impart free-flowing characteristics to granular explosives. For many uses, a high viscosity characteristic is generally preferred (Filbert, 1952).

Uses of Modified Starches in Pharmaceuticals

<u>Filler-Binder for Direct Compression</u>

Although starches are cheap and widely available excipients, their flow properties are insufficient for use as directly compressible filler-binders. Special starch products with both improved flow and binding properties as compared with native starches were therefore introduced.

The compression characteristics of modified rice starch (Primotab[R] ET) was evaluated by Bos et al. (1992). It was found to have excellent flow and binding properties. In contrast with other starch based filler-binders the binding properties stay sufficient after mixing with a hydrophobic lubricant. In tablet formulation, it can be used as unique filler-binder, which may be of benefit when drugs like primary amines are tabletted. Modified rice starch can also be combined with other filler-binders such as α-lactose monohydrate 100 mesh or anhydrous β-lactose. Combinations with microcrystalline cellulose should be avoided because of the poor flowability of the blends and the slow disintegration of the tablets.

Karr, Shiromani, Bavitz (1990) studied the binding efficencies of starch N.F. and modified starches in formulations of poorly water soluble drugs and found that binding efficiency was directly proportional to the granule coarseness which, in turn, was directly proportional to mean work of compression expended by the upper and lower punches for equally well-lubricated granulation. The formulations containing the

modified starches exhibited a faster release of low water soluble drug than the starch N.F. counterpart due to more uniform dispersion of modified starch binders.

Crosslinked starches have been evaluated on their potential use as binding agent in several studies. The pregelatinized starch and pregelatinized-crosslinked starches showed promising use as a binding agent in the conventional wet granulation process (Visavarungroj et al., 1990a) and high shear wet granulation process (Visavarungroj et al., 1990b). They were good binding agents for the granulation of lactose either in the dry form or as a paste. There was no difference, however, in binding properties between pregelatinized waxy corn starch and pregelatinized phosphate-crosslinked starch (Visavarungroj and Remon, 1991). In addition, the investigation in order to characterize and determine the possible use of crosslinked-modified starches as sustained release agent indicated that crosslinked-modified waxy corn starches, either pregelatinized or not, in comparison to purely pregelatinized waxy-corn starch are not suitable to use as hydrophillic matrix in sustained release formulation (Visavarungroj et al., 1990c).

The compressibility of various modified starches was evaluated in comparison with commercially available modified starches. The results showed that modified rice starch derived by physico-chemical treatments exhibited the high degree of compressibility and allowed rapid disintegration (Siriyos Timaroon and Poj Kulvanich, 1992; Wallop Weecharangsan, 1995).

Disintegrant

      Starch and starch derivatives are frequently used in tablets as disintegrant at concentration of 3-15% w/w. The mechanism of action of disintegrants in tablet has mainly been attributed to the swelling of the particles when they are brought into contact with water. A comparative evaluation of the properties of some tablet disintegrants, including those of starches and derivatives, has been reported by Gissinger and Stamm (1980). Among other results, it was found that carboxymethylstarches provided a very short disintegrating time and were the most efficient disintegrants (Wade and Weller, 1994; Thavisak Teruya, 1995).

      Soontorn Vorakul (1980) reported the disintegrating ability of carboxymethyl starch in sulfadimidine tablets. The amount of carboxymethyl starch required in the tablet was less than that of native starch. The optimum quantity of carboxymethyl starch in the granules was 5.0%

Bioadhesive Provider

      Bottenberg et al. (1991) utilized modified corn starch as a component in a fluoride-slow-release tablet with bioadhesive properties. The formulation that contained thermally modified corn starch along with 5% (w/w) polyacrylamide (PAA) and polyethylene glycol (PEG) with a molecular weight of 300,000 daltons proved to be the most suitable formulation for this purpose. The method was claimed to be a positive step in the development of dose-efficient fluoride administration in the oral cavity.

Carrier for Solid Dispersions

Chowdry and Venkateswara (1991) have evaluated modified starches, namely dextrin, cyclodextrin, and hydroxyethyl starch as carriers for solid dispersions of two poorly soluble drugs, phenylbutazone and nalidixic acid. The result indicated that modified starches were non-hygroscopic, non-interacting carriers giving solid dispersions and effective in increasing the dissolution rate and efficiency of the two poorly soluble drugs.

Microcapsule Preparation

Levy and Andry (1990) demonstrated that microcapsules could be prepared by using starch derivatives, including hydroxyethylstarch and carboxymethylstarch, as matrices. With these two starch derivatives, the resulting microcapsules could be lyophillized, giving free-flowing powders. The microcapsules were shown to be stable towards pepsin.

Dissolution Rate Enhancer

The ability of a low substituted N-octenylsuccinate starch as a dissolution rate enhancer of a poorly soluble drug, nifedipine, has been investigated by Ntawukulilyayo et al. (1993). The result showed that this modified starch could be considered as a powerful dissolution enhancer of drugs in solid dosage form.

Surfactant

Starches are highly polar polysaccharides that can be chemically modified to useful surfactants by reaction with acid chloride, for example, 2-chlorotriethylamine (Nash, 1988).

Topical Preparations

Starch is widely used in dusting-powders for its absorbency, and is used as a protective covering in ointment formulation applied to the skin. Starch mucilage has also been applied to the skin as an emollient, and formed the base of some enemas and has been used in the treatment of iodine poisoning (Nash, 1988).

Suspension

A suspension is a type of pharmaceutical dispersion in which an internal solid phase is uniformly dispersed throughout an external liquid or semisolid phase, called suspending vehicle. The internal phase, which consists of solid particles of active ingredients, is maintained uniformly in time throughout the suspending vehicle with the aid of a single or a particular combination of suspending agents. The application of suspension includes oral, topical, and parenteral dosage forms. Suspension is usually a pharmaceutical dosage form of choice when the drug or active ingredient is poorly soluble or insoluble in water (Nash, 1988).

For oral suspension, several characteristics are required in order to meet a satisfactory in formulation. The requirements are as follow (Martin, 1961);

1. Resuspension of drugs particles occurs readily upon shaking.

2. The dispersed particles must not settle too rapidly after shaking.

3. Resuspension produces a homogenous mix of drug particles such that the exact concentration of drug can be removed repeatedly.

4. During the shelf-life of the suspension no hard cake, too difficult to redisperse, will form.

5. The suspension maintains its stability, both chemically and physically, and elegance during its shelf-life.

6. The suspension possesses a taste that suites the acceptance of the patient.

Formulation of Suspensions

There are several problems associated with the formulation of an acceptable suspension. Suspension probably is the most difficult of all pharmaceutical dosage form to develop in terms of chemical and physical stability, elegance, formulation, and use. A number of components are required in order to prepare a physically stable suspension. Other than the drug itself, the basic components typically include;

1. wetting agent

2. dispersant or deflocculating agent

3. suspending agent (thickener or protective colloid)

4. buffer system

5. preservative

6. sweetener

7. flavor and coloring agent

8. liquid vehicle

Additional excipients may be used (e.g. osmotic agent), if necessary. Among all components, one most crucial factor in the preparation of a suspension is the selection of proper suspending agent (Nash, 1988).

Commonly Used Suspending Agents (Wade and Weller, 1994)

Suspending agents are used in formulation to provide the support network for the suspension vehicle and to maintain a uniform dispersion of particles that would otherwise settle rapidly to form a closely packed sediment and prevent the removal of an accurate dose (Scheer, 1981). Most commonly used suspending agents can be categorized under five broad headings: cellulose derivatives, clays, natural gum, synthetic gum, and miscellaneous compounds.

1. Cellulose Derivatives

Cellulose derivatives are semisynthetic compounds that are commonly used as suspending agents. These compounds, except sodium carboxymethylcellulose, are non-ionic and therefore are chemically compatible with most other ingredients. Combinations are used to increase suspending ability. Microcrystalline cellulose has been used in combination with hydroxypropyl, sodium carboxymethylcellulose, and methylcellulose. The combination of microcrystalline cellulose and sodium carboxymethylcellulose is used extensively. It dispersed quickly in cold water and needs little hydration time. The presence of sodium carboxymethylcellulose adds

sufficient structuring to retard sedimentation of the cellulose. The presence of the anionic derivative also extends the usefulness over a wide pH range.

Methylcellulose also produces gels and is available in several viscosity grades. This agent is soluble in cold and insoluble in hot water. It is dispersed in hot water and a subsequent temperature reduction dissolves this agent. Agents with properties and uses similar to those of methylcellulose includes ethylmethylcellulose and ethylhydroxyethylcellulose.

Sodium carboxymethylcellulose is extensively employed as a suspending agent. Since it is anionic; it is usually incompatible with cationic species. Hydroxypropylcellulose is soluble in both water and alcohol. This agent is pseudoplastic at high shear and has been used as a protective colloid. Water soluble cellulose derivatives are all subject to microbial degradation and require preservatives.

2. Clays

Clays are inorganic materials derived from natural sources; they are predominantly hydrated aluminum and/or magnesium silicates which in water hydrate furthur to form highly thixotropic gels. These agents should be dispersed in water with high shear for optimum dispersion and hydration. Clays are most stable between pH 9 and 11 but can be used within a broader pH range. The gels must be preserved with suitable antimicrobial agents since clays are liable to contamination with microbial spores. Ethanol and electrolytes may reduce the viscosity of these agents.

Magnesium aluminum silicate is used very extensively as a suspending agent, usually at a concentration between 0.5% and 2.5%. Its innocuous taste often produces a more acceptable suspension than other suspending agents. Equal concentrations of bentonite and sodium carboxymethylcellulose for a total of 5% produce a good structured vehicle.

3. Natural Gums

The natural gums include those of tree exudate, seed or root, and seaweed origin. These agents are nontoxic, readily available, and inexpensive. They are water soluble and produce solutions of high viscosity. Most are anionic and therefore are incompatible with cationic species. In addition, these agents are quite susceptible to bacterial and mold growth. Another disadvantage of natural gums is batch variation in color, viscosity, gel strength, and hydration rate. Due to these disadvantages and their anionic charge, other agents such as the cellulose derivatives are often preferred.

Agar, the alginates, and carrageenan are seaweed extracts. Dry agar is resistant to microbial growth and produces strong gels. Agar solutions demonstrate maximum stability at pH value between 4 and 10. Tragacanth solutions are very viscous and have been employed to suspend dense particles. Pectin solutions have low viscosity; use of this agent is decreasing. Guar gum and locust bean (or carob) gum are nonionic. Guar gum is recognized as producing solution of very high viscosity. A 1% aqueous dispersion has a similar viscosity to tragacanth mucilage. Guar gum is a poor suspending agent for insoluble powders. Tamarind gum, or specifically Tamarind seed

polysaccharide, is seldom used in the pharmaceutical industry although it is nonionic, disperse readily in cold water, and forms viscous solution at concentrations less than 2%. This agent is relatively unaffected by the pH of the solution. Xanthan gum is a high molecular weight natural polysaccharide produced from microbial fermentation by an organism originally isolated from the rutabaga plant. It has good batch-to-batch uniformity, few microbial contamination problems since it is unusually resistant to enzymes, and it is soluble in both hot and cold water.

4. Synthetic Gums

The synthetic agents include Carbomer and Povidone. Carbomer solutions have a very high viscosity and yield value. Povidone, which is polyvinylpyrrolidone, should be used with other suspending agents since it has a low solution viscosity. It is used more often as a protective colloid.

5. Miscellaneous

Gelatin is also used as a suspending agent. Solutions demonstrate marked variations in viscosity between batches; maximum stability is achieved at pH values between 5 and 8. Gelatin is stable in air when dry, but putrefies rapidly when moist or in solution.

Evaluation of a Suspension

There are many dimensions of a suspension dosage form that are indicative of its quality, acceptance, and performance. General appearance, color, odor, pH, density, viscosity, sedimentation volume, ease of redispersibility, particle size, dissolution, zeta potential, microbial integrity, labeled potency, and human safety are all important and useful parameters that provide guidance in evaluation procedures for suspensions. The following parameters are commonly evaluated when a suspension is formulated.

A. Sedimentation Volume

Sedimentation is an important factor in drug stability. The sedimentation rate, v, of spherical particles in a dilute suspension is described by a variation of Stokes's law shown in the following equation;

$$v = \frac{2r^2(\Delta\rho)g}{9\eta}$$

where $\Delta\rho$ = density difference between internal phase and continuous phase

g = acceleration due to gravity

η = viscosity of continuous phase

Experimentally, sedimentation volume can be determined from the ratio of the ultimate height (Hu) of the sediment to the initial height (Ho) of the total suspension as the suspension settles in a cylinder under standard conditions and the equilibrium has been reached. The larger this value, the greater is the degree of flocculation of the particles and the better is the suspendability (Martin, 1961). The cylindrical graduate

method is a simple, inexpensive, and standard-size tool for determining the sedimentation volume of a suspension. The method is done by making periodic measurement of sedimentation height without disturbing the system. Normally, the interpretation of result is achieved by plotting a graph between the Hu/Ho ratios and time. The different formulations can be compared by observing the lines, the better formulations produce lines that are more horizontal and/or less steep (Patel, Kennon, and Levinson, 1986).

B. Ease of Redispersibility

Redispersibility is one of the major considerations in assessing the acceptability of a suspension. It is defined as the ability to resuspend the settled particles with a minimum amount of shaking after a suspension was allowed to settle for some time (Nash, 1966). The determination was encountered by rotating the tubes containing the dispersions in a vertical plane about the midpoint of the tube, either by hand or by a rotaing machine (Rawlins and Kayes, 1983). The number of revolutions required to obtain a dispersion was recorded and was termed the redispersibility value (RV).

C. Rheological Measurements and Viscosity

Rheologic behavior of suspensions can be used to describe quantitatively the flow behavior of a material for the purpose of quality control, to determine the settling behavior, the arrangement of the vehicle and particle structural features, to quantitate the effects of time, temperature, ingredients, and processing parameters on a formulation, as well as to understand the overall performance characteristics and the

fundamental nature of a product system for purposes of comparison (Patel, Kennon, and Levinson 1986). In particular, a suspension that possesses high thixotropic value is the most preferable.

D. Zeta Potential Measurement

The determination of the zeta potential of particles in a suspension provides useful information concerning the sign and magnitude of the charge and its effect on the physical stability of the system with time (Nash, 1988). Studies indicated that certain zeta potentials produced more stable suspensions because aggregation was controlled and optimized.

Rheology and Application in Pharmaceutical Products

Rheology is the science which deals with deformation of a body under the influence of stress. Bodies in this context can be solids, liquid, or gases. Ideal solids deform elastically. The energy of deformation is fully recovered when the stresses are removed. Ideal fluids such as liquids and gases deform irreversibly - they flow. The end of deformation is dissipated into the fluids in the form of heat, and it cannot be recovered just by releasing stresses. The real bodies we encounter are neither ideal solids nor ideal fluids. Rheology is involved in the mixing and flow of materials, removal prior to use, and packaging into containers. Its applications in pharmacy are wide ranging including liquids, semi-solids, gel, solid deformation, coating, and packaging materials.

In suspension formulation, the rheology of the suspending agent usually dominates the overall properties of the suspension. A study showed that an ideal suspending agent should be shear thinning, should have a high viscosity at low shear for shelf stability and a low viscosity at high shear for easy dispensing (Deem, 1988).

The Basic Law of Viscosity

To measure the viscosity of liquids requires first the definition of the parameter which are involved in the flow. Then one has to find suitable test conditions which allow the measurement of flow properties objectively and reproducibly.

Isaac Newton was the first to find the basic law of viscometry describing the behaviour of an ideal liquid;

$$\text{Viscosity } (\eta) = \frac{\text{shear stress (T)}}{\text{shear rate (D)}}$$

Shear stress

An internal force (F) applied to an area (A) being the interface between the upper plate and liquid underneath leads to a flow in the liquid layer. The velocity of flow that be maintained for a given force will be controlled by the internal resistance of liquid, i.e. by its viscosity.

$$T = \frac{F \text{ (force)}}{A \text{ (area)}} = \frac{N \text{ (Newton)}}{m^2} = Pa \text{ (Pascal)}$$

The SI unit "Pascal" (Pa) has replaced the former unit "dyne/cm^2" which had previously been used for stresses especially in scientific literature. One pascal equals 10 dyne/cm^2.

Shear rate

The shear stress (T) causes the liquid to flow in a special pattern. A maximum flow speed v_{max} will be found at the upper boundary. The speed drops across the gap size y down to $v_{min} = 0$ at the lower boundary contacting the stationary plate. Laminar flow means that minute thin liquid layers slide on top of each other, similar to cards in a deck-of-cards. One laminar layer is then displaced with respect to the adjacent ones by a fraction of the total displacement encountered in the liquid between both plates.

In its general form the shear rate (D) is defined by a differential;

$$D = \frac{dv}{dy}$$

when v is velocity (m/s) and y is distance (m). Therefore, the unit of shear rate is;

$$D = \frac{m/s}{m} = \frac{1}{s} = (s^{-1})$$

Flow and Viscosity Curves

The correlation between shear stress and shear rate defining the flow behavior of a liquid is graphically displayed in a diagram of T on the ordinate and D on the abscissa. This diagram is called the "Flow Curve". The most simple type of a flow curve is shown below. The viscosity is assumed to be constant and independent of D.
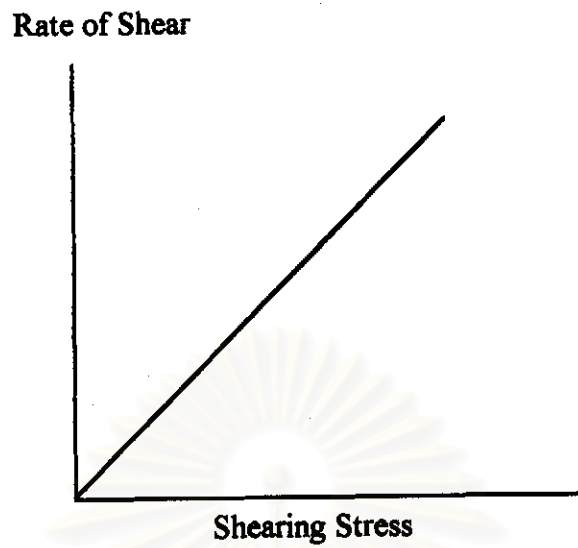
Rate of Shear

Shearing Stress

Figure 4   Flow Curve of a Newtonian Liquid

Another diagram is very common: v is plotted versus D. This diagram is called

the "Viscosity Curve".
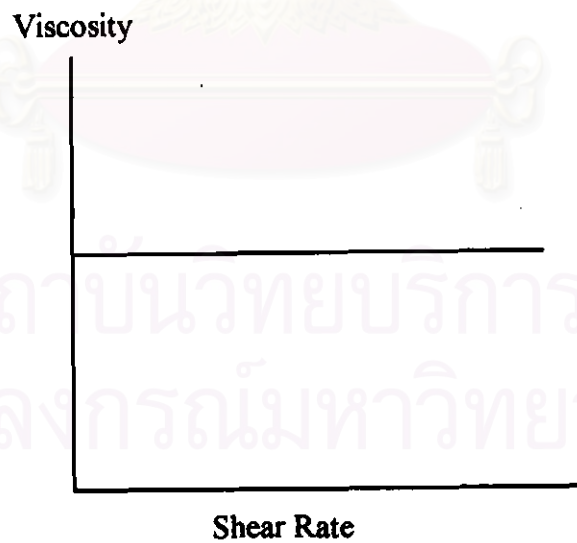
Viscosity

Shear Rate

Figure 5   Viscosity Curve of a Newtonian Liquid

Viscosity measurement lead always first to the flow curve. Its results can then be rearranged mathematically to allow plotting the corresponding viscosity curve. The different types of flow curves gave their counterparts in types of viscosity curves.

Flow Characteristics of Fluids (Deem, 1988)

Newtonian Flow

Newton recognized that the rate of flow of a liquid is proportional to the stress (F) applied, the constant of proportionality is called the (dynamic) viscosity (η). The kinematic viscosity is the dynamic viscosity divided by the density of the liquid. Some examples of typical Newtonian liquid include water, mineral oils, bitumen, mollasses.

The viscosity of a dilute solution (η) is always greater than of the solvent (η_0) so that the relative viscosity (η_r) is;

$$\eta_r = \frac{\eta}{\eta_0}$$

Non-Newtonian Flow

It is now recognized that adherence to Newton's law is relatively uncommon. Flow behaviors that deviate from Newtonian are called "non-Newtonian". The essentail characteristics of a non-Newtonian system is that the viscosity is not directly proportional to the shear rate. Several types of non-Newtonian rheological behavior were identified.
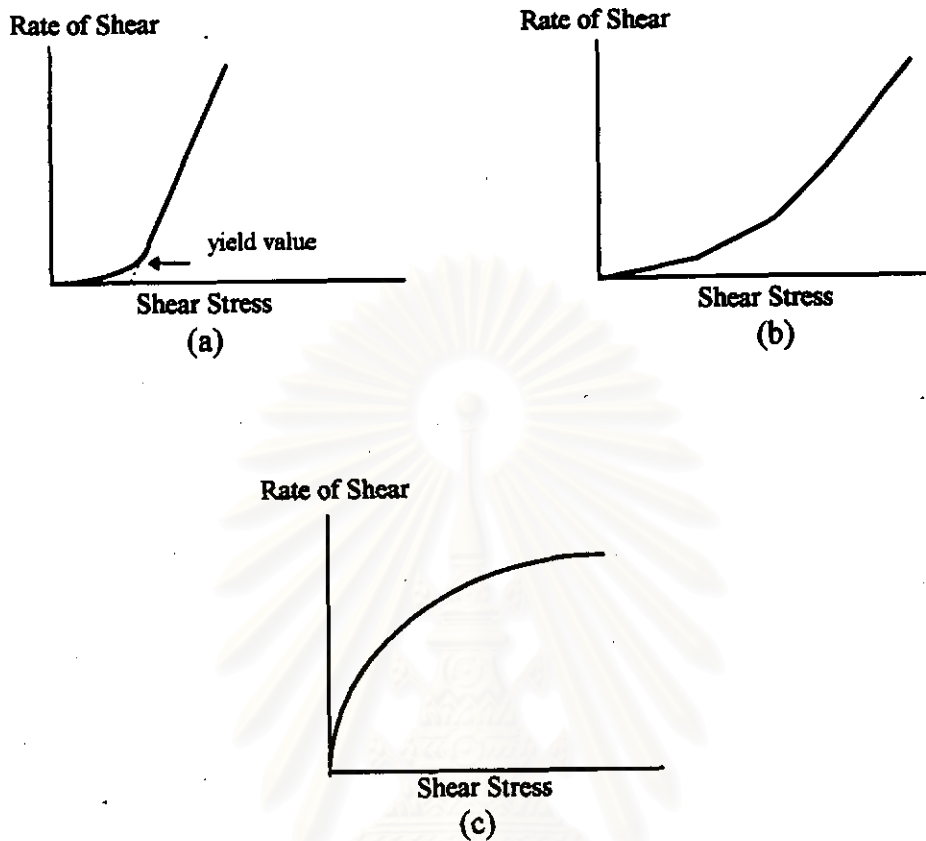
Rate of Shear

yield value ←

Shear Stress

(a)

Rate of Shear

Shear Stress

(b)

Rate of Shear

Shear Stress

(c)

Figure 6   Typical non-Newtonian Flow Curves

Plastic Flow

This is sometimes called Bingham flow and a material showing it is called a Bingham body. The most important characteristic of plastic flow is the existence of a yield value, an intercept of a straight line on the shear stress axis (Figure 6a), which implies solid-like behavior under quiescent conditions (Zatz, 1985). This has the advantage of locking particles into a rigid network, which may effectively inhibit sedimetation altogether. Agitation temporarily disrupts the network, making it possible to do such things as shake, pour, or spread a preparation onto the skin.

Pseudoplastic flow

The rheogram of a pseudoplastic system is usually a smooth curve (Figure 6b). Since the slope of the line represents the viscosity, it can be seen that the material becomes thinner the faster it is stirred. For this reason pseudoplastic flow is sometimes called shear rate thinning. In this type of flow the rate of shear is not directly proportional to the shearing stress. The curve pass through the origin, but is rarely linear. Pseudoplastic flow is characteristic of most natural and synthetic gums.

Dilatant Flow

Dilatant flow is characteristic of some products containing high levels of deflocculated solids, such as oil slurries and muds. In this type of flow, an increase in viscosity is observed as the rate of shear is increased (Figure 6c)(Ward, Kinney, and Saad, 1974).Dilatant flow behavior is found, for example, in highly concentrated suspensions in which solid particles are mixed with liquids such as plasticizers. The particles are densely packed and the amount of plasticizer added is just sufficient to fill the voids between the particles. At rest or at low coating speeds the plasticizer fully lubricates the particle surfaces and thus allows an easy positional change of particles when forces are applied: this suspension behaves as a liquid at low shear rates. At higher shear rates particles will wedge others apart causing a general volume increase of the plastisol. At this stage the plasticizer's share of the total volume decreases. No longer being sufficient to fill all voids and to keep particle surfaces fully lubricated the plastisol becomes more viscous (Schramm, 1981a). Dilatant flow can occur when the

ratio of the solid phase to the liquid phase is large. This flow type can be observed in paints, inks, or concentrated starch pastes (Deem, 1988).

Thixotropy

Thixotropy is a rheological phenomenon of great industrial importance and is frequently observed in suspensions. It is described as a breakdown and reforming of the gel/sol/gel structure. A typical rheogram for a thixotropic material is shown in Figure 7, where as the rate of shear is increased the ratio of stress to shear continually decreases. If at any point along the upcurve the rate of shear is decreased rapidly no further change in consistency is noted, and an hysteresis loop is formed. The decrease in consistency differs from that seen with pseudoplastics in that there is a finite time required for reformation of sufficient yield value and viscosity, so that the shearing will produce a thinning which is persistent after shearing is discontinued. Thinning has been found to occur with increased rate of shear and with time of shear at any given rate. Thixotropy is a desirable characteristic in liquid pharmaceutical systems that ideally should possess a relatively high consistency in the container, yet easily to pour or spread. A well-formulated thixotropic suspension will not settle out readily in the container, will resuspend upon shaking, and will remain long enough for an accurate dose to be withdrawn. Finally it will regain consistency rapidly enough so as to maintain the particles in a suspended state (Schramm, 1981b). Thixotropic behavior can be observed in gelatin, latex paint, and emulsion systems (Deem, 1988).
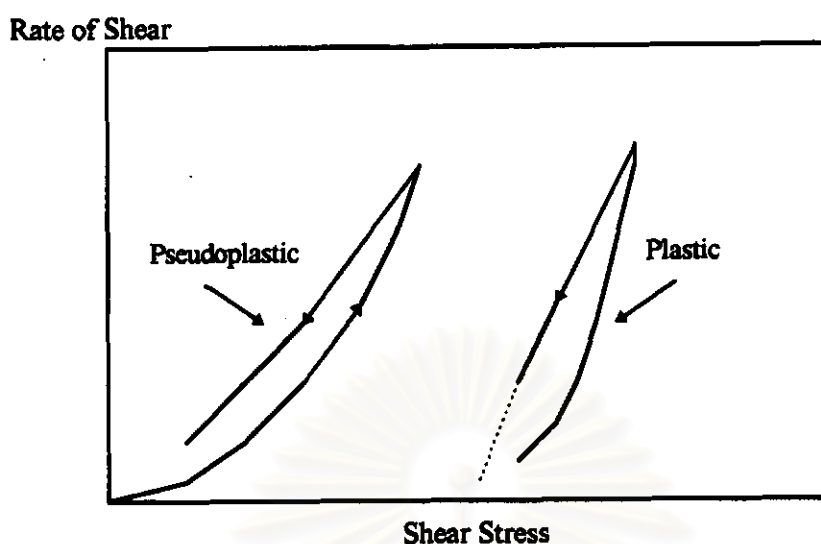
Rate of Shear

Figure 7   Rheogram of Thixotropic Material

Rheopexy

Rheopexy is a phenomenon in which a sol forms a gel more readily when gently shaken or otherwise sheared that when allowed to form the gel while the material is kept at rest. The term "negative thixotropy" is sometimes used to define rheopexy. The behavior is characterized by a viscosity increase related to the two duration of shear. When these liquids are allowed to rest they will recover the original, i.e. the low, viscosity level. Rheopective liquids can cycle infinitely between the shear time related viscosity increase and the rest time related decrease of viscosity. Rheopexy and thixotropy are opposite flow properties. This can also be seen in the sense of the hysteresis of the flow curve, i.e. where the upcurve is positioned in relation to the downcurve. Rheopective liquids show a counter-clockwise sense: The downcurve comes back above the upcurve. Thixotropic liquids have downcurves well below the upcurve. Magnesia magma and clay suspensions are among the rare example of this phenomenon (Schramm, 1981b).

Quantitative Measurement of Thixotropy

As mentioned earlier, thixotropy is a preferred characteristic of pharmaceutical dispersion system, including suspension. Therefore, several procedures have been proposed to characterize and measure the quantity of a thixotropic sample. The most apparent characteristic of a thixotropic system is the hysteresis loop, formed by the up- and down-curve of rheogram (Figure 8). The area of this loop represents a so-called "thixotropic breakdown", the energy that is required to breakdown the thixotropic structure. The value can be obtained readily by means of a planimeter, computer integration or other suitable techniques.
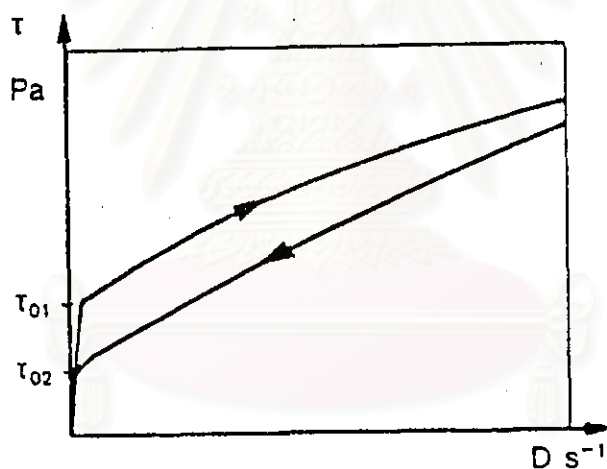
Figure 8   Hysteresis Loop

Rotational Viscometer

Rotational viscometers with coaxial cylinder or cone and plate sensor systems are very well suited for determining the flow behavior of high and low viscosity, Newtonian- and non-Newtonian liquids. The Rotovisco viscometer (Figure 9) is an example of this type of viscometer. These viscometers are excellent for characterizing

pseudoplastic and dilatant samples. They can also be used to determined thixotropic characteristics of a material by recording the torque values as a function of time with the instrument rotating at a constant angular velocity (Deem, 1988). Rotational viscometers are a very good choice for research work and quality control purposes under rugged factory conditions.
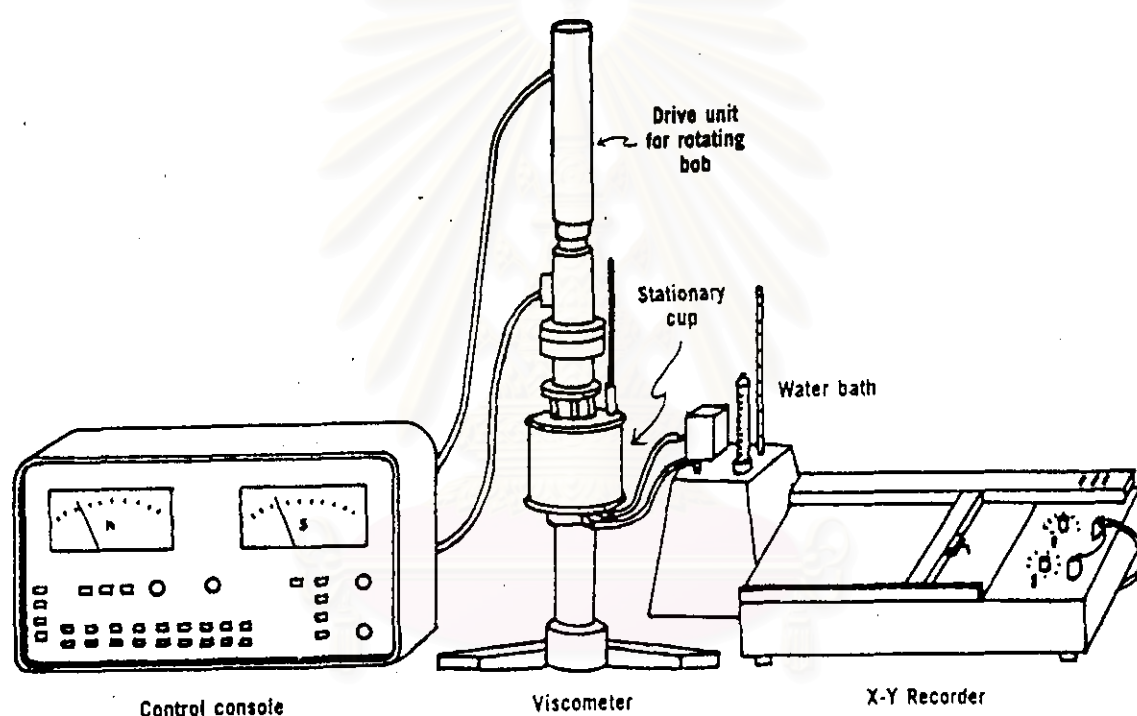

Figure 9   Haake Rotovisco Viscometer

In the measurement of liquid viscosity by means of this instrument, the sample is placed into the annular gap between an outer cylinder and the inner cylinder or cone. As illustrated in Figure 10, a motor (M) drives the inner cylinder or cone (R). A viscosity related torque, caused by the resistance of the sample to shearing, acts on the

inner cylinder or cone. The torque deflects a measuring spring placed between the

motor and the inner cylinder or cone. The size of the spring deflection correlates

linearly with the generated stress which is measured as a torque. The spring deflection

is transformed into an electric signal and shows up as digital indication on the recorder.
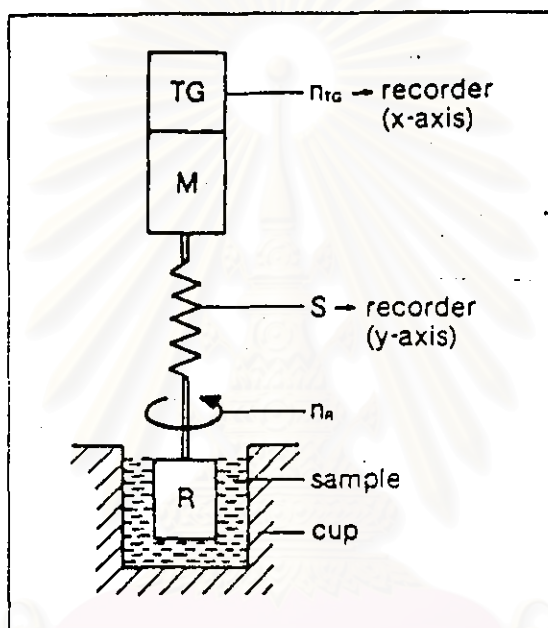

Figure 10   Schematic Illustration of a Rotational Viscometer (Schramm, 1981a)

The speed signal required for the determination of the shear rate plotted on the

abscissa of flow curves does not come from the rotor directly but rather from the

tacho-generator (TG) which sits above the motor and is mechanically linked to it.

Under normal test conditions for plotting the flow curves of liquids, the speeds of both

the tacho-generator and motor, as well as the rotor, are identical so that the speed

signal n_{TG} also defines the rotor speed n_R (Schramm, 1981a).